REMARKS

These remarks are in response to the Office Action dated September 10, 2003. Claims 1-34 have been canceled. New claims 35-54 have been added. Support for the new claims can be found throughout the specification and is specifically identified in the body of the present Response. In addition, a declaration from Dr. Noriyuki Kasahara accompanies the present Response. No new matter has been added.

Claims 35-54 are pending and at issue. Applicants respectfully request reconsideration of the present application.

SEQUENCE DISCLOSURE RULE COMPLIANCE

Applicants hereby submit that the enclosures fulfill the requirements under 37 C.F.R. §1.821-1.825. Applicants submit herewith a Sequence Listing in computer-readable form as required by 37 CFR §1.824. In addition, applicants submit a substitute Sequence Listing as required under 37 CFR §1.823(a) and a statement under 37 CFR §1.821(f). The amendments in the specification merely insert sequence identifiers in the specification, and replace the original Sequence Listing with an amended substitute Sequence Listing. The substitute Sequence Listing contains the nucleic acid sequences depicted in Figures

1B and 9B, now SEQ ID NOs:1-3, respectively. No new matter has been added.

I. PROVISIONAL REJECTION UNDER 35 U.S.C. §101

Claims 1-34 stand provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 41-46, 49-51, 56, 58-61 and 63-82 of co-pending Application No. 10/045,178 ('178). Applicants note that this rejection is moot with regard to canceled claims 1-34. Further, the Examiner can maintain the provisional rejection in the present application until it is the only rejection remaining and the '178 application is still pending (MPEP §804, part IB). When that case arises, the Examiner must withdraw the rejection in the present application and permit it to issue as a patent.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-34 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. This rejection is moot with regard to canceled claims 1-34. Applicants respectfully traverse this rejection as it may be applied to the pending claims.

Applicants respectfully submit that the originally filed application provides ample support for the scope of the pending claims. The methods of the invention are based on Applicants' discovery that novel replication competent retroviral vectors could be used to enhance the efficiency of transduction in vivo. The novel vectors utilize a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug (see new claim 35). The cassette is positioned 3′ to the sequence encoding the retroviral envelope and 5′ to the 3′ LTR sequence of the retroviral genome. Example 1 describes the construction of the vector and the insertion of the IRES-transgene into a position in the viral genome that enhanced the stability of the insert while linking expression of the inserted transgene to viral coding sequences (see page 55, Example 1; see also page 56, lines 17-25). The IRES sequence was inserted just downstream from the envelope message but upstream from the 3' LTR (see Figure 2; see also page 57, lines 4-19). The specification, beginning at page 64, lines 8-25, bridging to page 58, lines 1-3, describes how the novel vector is capable of retaining and delivering a transgene encoding green fluorescence protein (GFP) to practically all cells in culture even with low initial

transduction levels. At page 58, lines 1-5, the specification describes the replacement of the GFP transgene with a sequence encoding a polypeptide that converts a pro-drug in to a toxic drug, such as the Herpes simplex virus thymidine kinase (HSV-tk) gene and the E. coli purine nucleotide phosphorylase (PNP) gene. Example 18 (page 91) describes the construction of a vector harboring such a sequence. Example 19, describes the use of such a vector in a culture of carcinoma cells.

A declaration by Dr. Noriyuki Kasahara under 37 C.F.R. §1.132 accompanies the present response. The declaration describes the manner in which one skilled in the art of gene therapy can use the method of the invention, in conjunction with the disclosed vectors, to treat a cell proliferative disorder. Specifically, the declaration provides data that clearly indicates the method of claim 35 can be used to treat a cell proliferative disorder (e.g. glioblastoma). The vector used in the treatment is the same vector described in the preceding paragraph and disclosed in the specification. The declaration provides data that indicates that a therapeutic effect can be achieved by the methods and vectors described in the specification; i.e., that delivery of a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic

prodrug to a toxic drug to neoplastic cells in a subject provides a therapeutic effect.

Applicants further note that the data provided in the accompanying declaration utilize nude mice as a model for human neoplastic disorders. The use of immunocompromised animal models were useful for at least two reasons. First, Applicants utilized human neoplastic tissue implanted in animal models to provide support for the therapeutic benefit of the present invention to human cell proliferation disorders. The human neoplastic xenografts implanted in the immunocomprised animals would have been immediately rejected if implanted in immunocompetent animals, rendering the experimental model for identifying transduction and horizontal infection by RCR viruses in a human tumor model entirely useless. Second, even if a mouse tumor, as opposed to a human tumor, were induced to form in an immunocompetent mouse, an immune response mounted by such an animal against an RCR virus of the invention may have the secondary effect of provoking an immune response against the tumor. Again, any results derived from this experiment could be interpreted as simply an activation of the host immune system by the introduction of RCR virus. Such results would be marginal or may be uninterpretable with regard to RCR viral transduction. Applicants submit that, absent the use of a human tumor in a

human model, the best available animal model was used to generate a working example correlative to human RCR viral therapy.

Applicants further submit that the Training Materials for Examining Patent applications, with respect to enablement for chemical-biotechnical applications, has addressed the use of experimental animal models and concluded that "an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" because that example "correlates" with a disclosed or claimed method invention." The Training Materials further state that "the evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." In addition, the courts have weighed-in on the issue, concluding that a rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> ... based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

New claim 52 is directed to a method of treatment using a vector comprising a "tissue-specific promoter sequence contained within the LTR sequences" of the genome of the replication competent retroviral (RCR) vector. Applicants note that this

vector incorporates a mechanism for specifically allowing replication of the RCR vector in a tissue that supports transcription of the "tissue-specific" sequence (see Examples 5-7, beginning at page 66). Nevertheless, this vector retains the same novel IRES-transgene sequence described above.

New claim 52 is directed to a method of treatment using a vector comprising a nucleic acid sequence encoding a retroviral envelope comprising "a chimeric env protein comprising a targeting ligand." Applicants note that this vector incorporates a mechanism for specifically targeting a particular tissue for infection by the RCR vector by incorporating a ligand in the viral. This allows the RCR vector to target, for example, breast cancer cells (see Examples 2-4, beginning at page 61). Similar to the "transcription-specific" vector, this vector retains the same novel IRES-transgene sequence described above.

The Office Action appears to take the position that the art of gene therapy for treating cell proliferative disorders is highly unpredictable. In support of this, the Office Action cites to various publications and reports that allegedly describes the state of the art of gene therapy at the time the present application was filed. In contrast to the references

cited by the Office Action, reports drafted in the same, or nearly the same, time period indicate that:

> Enough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic responses that are relevant to human disease, and can provide important insights into human biology...accomplishments to date are impressive, and the logic of the potential usefulness of this clinical paradigm continues to be compelling.

(See Crystal, Science, 270:404, 1995).

For example, Applicants point to a recent publication that states that gene therapy was used to treat malignant brain tumors (see Ram *et al.*, "Therapy of malignant brain tumors by intratumoral implantation of retroviral vector-producing cells," Nat Med, 3:1354-61, 1997). This publication provides evidence that intratumoral implantation of murine cells modified to produce retroviral vectors containing the herpes simplex virus-thymidine kinase (HSV-TK) gene induces regression of experimental brain tumors in rodents after ganciclovir (GCV) administration.

Further, the Office Action cites to Gomez-Navarro as supporting the concept that transduction efficiencies are notoriously inadequate for vectors used in gene therapy methods (see Office Action, page 4, beginning at line 5). Applicants note that the vectors used in the presently claimed methods address precisely these issues. The present vector is

"replication competent" and achieves transduction and expression efficiencies never achieved by previous vectors (see e.g., Example 9, page 76; Example 12, page 81; Example 13, page 84; and Example 19, page 91). Consequently, Applicants submit that statements contained in the Office Action regarding the "shortcomings" of current gene therapy methods may be accurate for those methods utilizing non-replication competent vectors, but are not accurate for methods employing the RCR vectors disclosed in the present application.

Applicants submit that one of skill in the art could readily identify, without undue experimentation, additional heterologous nucleic acid sequences for introduction into a replication competent recombinant retroviral (RCR) vector of the invention, as well as routes of administration and therapeutic dosages that would be applicable in the method of the present invention. With regard to dosage, §608.01(p) of the MPEP states that, "It is not necessary to specify the dosage or method of use if it is obvious to one skilled in the art that such information could be obtained without undue experimentation." The law therefore does not require recitation in a therapeutic method claim of how a vector (or genetically modified cell) is to be administered when a person of ordinary skill in the art could determine the most proper administration route without

undue experimentation. Nevertheless, Example 8 and Example 9 of the present specification provide examples of transduction and intratumoral spreading of the viral vector, including routes of administration and multiplicity of infection (MOI) calculations. Applicants note that the invention is the first to provide an RCR vector capable of "horizontal" infection through a targeted tissue for delivery of a therapeutic agent. One of skill in the art can easily determine the amount of vector necessary to elicit a therapeutically-effective response given that even a minimal amount of the vector will be sufficient to allow for horizontal infection of specifically targeted cells.

Applicants submit that, in light of the information contained in the present specification and in view of the level of skill in the art of gene therapy, it would not require undue experimentation to practice the invention. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

In summary, for the reasons set forth herein, Applicants maintain that claims 35-54 clearly and patentably define the invention. Applicants request that the Examiner reconsider the various grounds set forth in the Office Action and allow the claims that are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 678-5070. Please charge any fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

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